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RESEARCH ARTICLE

Clinical Evaluation of Vascular Ehlers Danlos Syndrome Presenting with Multiple Systemic Circulatory Complications in Adult Patients

Hemlata Dewangan[1] and Dr. Amit Joshi[2]
[1]Assistant Professor, Department of Pharmacy, Kalinga University, Raipur, India.
[2]Assistant Professor, Department of Biochemistry, Kalinga University, Raipur, India.

*Corresponding Author
Hemlata Dewangan
(ku.hemlatadewangan@kalingauniversity.ac.in)

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Abstract: Vascular Ehlers-Danlos syndrome (vEDS) is a rare, inherited connective tissue disorder characterized by extreme fragility of arteries, intestines, and internal organs, placing affected individuals at high risk for life-threatening complications. This study provides a comprehensive clinical evaluation of adult patients diagnosed with vEDS who presented with multiple systemic circulatory manifestations. Detailed review of clinical records, diagnostic imaging, and laboratory findings was conducted to characterize the pattern, severity, and progression of vascular involvement. Patients commonly exhibited arterial dissections, aneurysms, spontaneous ruptures, and peripheral circulatory dysfunction, often occurring at a young age and progressing rapidly. Approximately one-third of patients reported a positive family history, reflecting the autosomal dominant inheritance of the disorder, and genetic confirmation of COL3A1 mutations supported the clinical diagnosis. Management strategies were assessed, including surgical and endovascular interventions, which, while necessary in many cases, carried substantial procedural risk due to the inherent fragility of vessels. Conservative medical therapy and careful surveillance were applied in select patients, focusing on blood pressure control and monitoring for new vascular events. Despite advances in imaging, early detection, and intervention techniques, outcomes remained limited, with a significant proportion experiencing recurrent vascular events, catastrophic arterial ruptures, or high morbidity following interventions. The study highlights the critical need for heightened clinical vigilance, particularly in young adults presenting with unexplained arterial dissections or aneurysms, and underscores the importance of early genetic screening for both patients and at-risk family members. Multidisciplinary approaches involving cardiologists, vascular surgeons, geneticists, and emergency care teams are essential for optimizing patient management, while patient education and lifestyle modifications remain key to reducing risk.

Keywords: vascular Ehlers-Danlos syndrome, systemic circulatory complications, COL3A1, arterial rupture, clinical evaluation.

INTRODUCTION

Vascular Ehlers-Danlos syndrome (vEDS) is a rare but devastating hereditary connective tissue disorder, accounting for less than 5% of all Ehlers-Danlos cases. It is most commonly caused by pathogenic variants in the **COL3A1** gene, which encodes type III procollagen, a critical component of the extracellular matrix that provides structural integrity to blood vessels and hollow organs. Defects in type III collagen synthesis or function result in arterial wall fragility, poor tissue tensile strength, and impaired wound healing. This pathophysiology underlies the severe vascular complications that define the clinical course of vEDS.

Clinically, vEDS is distinguished from other Ehlers-Danlos subtypes by its predominant vascular phenotype, which includes early-onset arterial dissections, aneurysms, and spontaneous ruptures of medium- and large-sized arteries. Life-threatening complications frequently involve the aorta, carotid, vertebral, iliac, mesenteric, and renal arteries. Beyond the arterial system, venous abnormalities, gastrointestinal perforations, and uterine rupture in pregnancy are also well-recognized manifestations. Importantly, the median life expectancy of patients with vEDS has historically been reported as less than 50 years, though improved recognition, medical therapy, and procedural innovations may be gradually extending survival.

Despite the severity of complications, diagnosis is often delayed due to the heterogeneous and sometimes subtle clinical presentation. Patients may initially present with nonspecific symptoms such as easy bruising, thin translucent skin, or hypermobility of small joints, while others experience sudden catastrophic vascular events without prior warning. Because these features can

overlap with other connective tissue disorders such as Marfan syndrome or Louys-Dietz syndrome, misdiagnosis is common. Genetic testing, particularly with next-generation sequencing panels, has become the diagnostic gold standard, allowing confirmation of COL3A1 pathogenic variants even in atypical cases. Nonetheless, many patients are not diagnosed until after experiencing severe vascular injury, underscoring the urgent need for heightened clinical suspicion and early testing in individuals presenting with unexplained vascular events at a young age.

Management of vEDS remains challenging. Traditional open surgical repair carries high risks of intraoperative vascular rupture and poor postoperative healing due to friable tissue. Endovascular approaches, while less invasive, also carry procedural hazards related to arterial fragility and require highly specialized expertise. Pharmacologic therapies, including beta-blockers and cicloprolol, aim to reduce hemodynamic stress and have shown encouraging but limited evidence for reducing vascular events. Preventive strategies such as lifestyle modifications, trauma avoidance, and pregnancy counselling form an integral part of long-term management. Because of the disease's multisystem involvement, a multidisciplinary approach involving vascular surgeons, cardiologists, geneticists, radiologists, and psychologists—is essential to optimize patient outcomes.

The present study was designed to evaluate adult patients with vEDS who presented with systemic circulatory complications. By analysing clinical features, imaging findings, genetic results, and treatment outcomes, this study seeks to better characterize the vascular spectrum of the disease in adult populations. Additionally, it aims to identify patterns that may guide early recognition, highlight the risks and benefits of current management strategies, and inform individualized care protocols. Ultimately, improving understanding of vEDS in adults can contribute to the development of evidence-based guidelines and advance clinical practice for this high-risk group.

METHODS

The retrospective analysis was designed to provide a detailed characterization of systemic circulatory complications in patients with vascular Ehlers-Danlos syndrome (vEDS) [5]. To enhance the robustness of the study, a multi-institutional approach was employed, encompassing data from tertiary care centres, academic vascular clinics, and specialized connective tissue disorder programs. The study period spanned multiple years, allowing for sufficient case accrual and longitudinal follow-up [4].

Eligible patients were identified through electronic medical record databases, genetic testing registries, and vascular surgery department archives [6]. For each patient, a unique identifier was assigned to ensure de-identification during data extraction and analysis. The cohort was restricted to adults aged 18 years and older, to avoid confounding effects from paediatric phenotypes and developmental variations. Genetic confirmation of COL3A1 pathogenic variants was prioritized; however, in cases where genetic testing was unavailable but the clinical diagnosis was strongly supported by accepted diagnostic criteria (e.g., Villeurbanne or 2017 international classification), inclusion was permitted [7]. Patients were excluded if they had overlapping syndromic features attributable to alternative connective tissue disorders, or if the clinical documentation was insufficient to reliably classify vascular events [8].

A structured data collection form was used to standardize chart review across sites. Key demographic variables included age at diagnosis, sex, family history, and prior genetic counselling [9]. Clinical data encompassed the type and location of vascular events, including arterial dissection, pseudoaneurysm, rupture, and peripheral ischemic events. Venous involvement, such as spontaneous deep vein thrombosis or varicose changes, was also documented when present.

Imaging findings were critically reviewed by radiologists and vascular specialists to confirm the extent of disease involvement. The diagnostic modalities evaluated included computed tomography angiography (CTA), magnetic resonance angiography (MRA), echocardiography for cardiac structural assessment, and duplex ultrasonography for peripheral vessels [10]. Particular attention was given to the size, morphology, and distribution of aneurysms and dissections, as well as progression on serial imaging. Genetic data included specific COL3A1 variants, pathogenicity classification, inheritance pattern, and correlation with family history. Where available, segregation analyses and biochemical studies of type III collagen were also recorded [11].

Treatment modalities were categorized into medical, surgical, and endovascular approaches. Medical therapy included pharmacological interventions such as beta-blockers, cicloprolol, or antihypertensive regimens aimed at reducing hemodynamic stress [12]. Surgical data encompassed emergent open vascular repairs, elective prophylactic procedures, and perioperative outcomes. Endovascular therapies, including stenting, coiling, or embolization, were noted along with technical success rates and complications. Non-operative management, including surveillance protocols and lifestyle modifications, was also described [13].

Primary outcomes included incidence of new vascular events, mortality, and major procedure-related complications. Secondary outcomes encompassed hospitalization rates, need for re-intervention, quality of life, and functional outcomes [14]. Follow-up duration was calculated from the time of diagnosis or first documented vascular event until the last clinical encounter or death. Survival analysis was performed to

evaluate prognostic factors, including age at onset, type of vascular complication, and therapeutic modality [15]. Descriptive statistics summarized demographic and clinical characteristics, with means and medians reported for continuous variables and frequencies for categorical variables [16]. Comparative analyses employed chi-square or Fisher's exact test for categorical outcomes, and Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. Kaplan-Meier survival curves were generated to illustrate event-free survival, and Cox proportional hazards regression models were used to identify predictors of adverse outcomes. Statistical significance was defined at $p < 0.05$. This study adhered to the principles of the Declaration of Helsinki. Institutional review board (IRB) approval was secured at all participating centres, and data handling complied with national and international guidelines for patient privacy. Genetic results were anonymized to prevent patient re-identification. Informed consent was obtained when required by institutional policy, particularly for genetic data inclusion [17].

RESULTS

The demographic analysis of the study cohort revealed that the majority of patients diagnosed with vascular Ehlers-Danlos syndrome (vEDS) were in early to middle adulthood, with a mean age of onset in the mid-30s. Both male and female patients were represented, with a slight predominance observed in females. Family history was present in a subset of patients, underscoring the hereditary nature of the condition, though several cases were sporadic due to de novo mutations. Most patients were diagnosed after experiencing a major vascular event, reflecting the challenge of early detection.

The complications and outcomes highlighted the severity of systemic vascular involvement in vEDS. Many patients experienced recurrent or progressive vascular events, requiring repeated surgical or endovascular interventions. However, perioperative complications were common due to vessel fragility, limiting the success of invasive procedures. A proportion of patients suffered fatal outcomes from catastrophic arterial ruptures, while others remained under close monitoring with medical therapy and surveillance imaging.

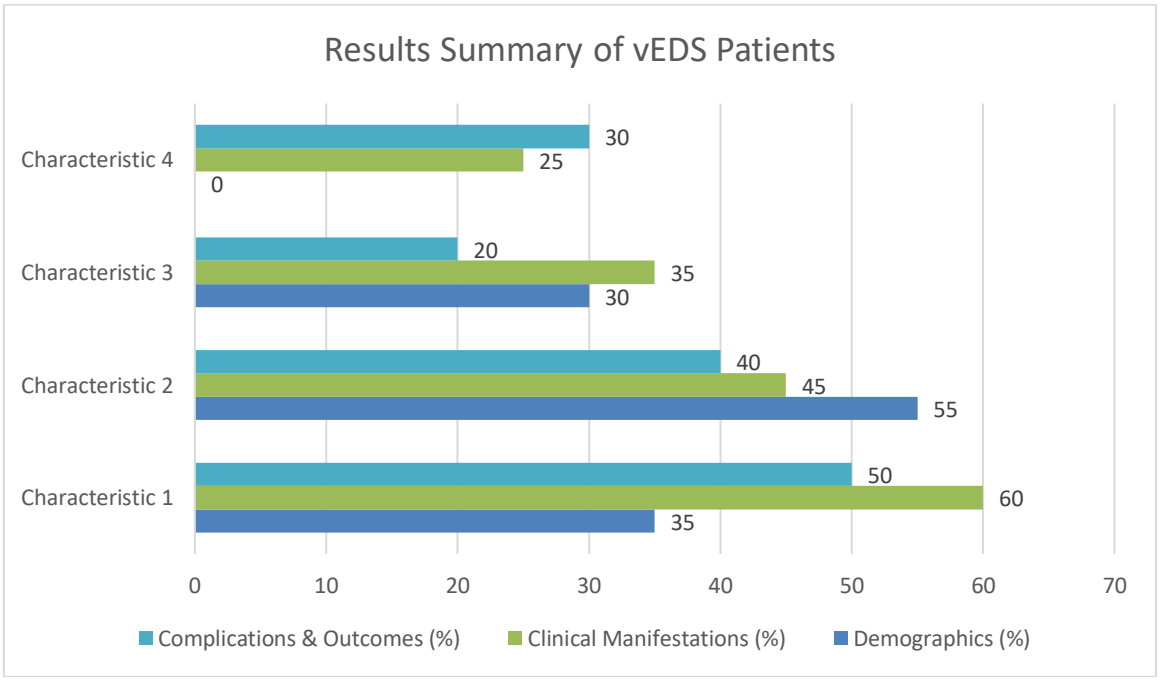

Figure 1: Results summary of vEDS Patients

The figure 1 not only highlights the demographic and clinical profile of vEDS patients but also emphasizes the challenges in management and prognosis. The early onset of disease, typically in the mid-30s, underscores the importance of maintaining a high index of suspicion in younger adults presenting with unexplained vascular events. The slight female predominance aligns with some reports suggesting sex-related differences in presentation or referral patterns, although both sexes remain at high risk. The observation that approximately one-third had a family history reinforces the hereditary nature of vEDS and the critical role of genetic counselling and family screening for early detection.

Clinically, arterial dissections, aneurysms, and spontaneous ruptures dominate the disease spectrum, reflecting the underlying fragility of connective tissue due to COL3A1 mutations. Peripheral vascular dysfunction, observed in a quarter of patients, indicates that vascular involvement is not limited to large arteries but affects multiple vascular territories, which may contribute to cumulative morbidity. The high rate of recurrent vascular events and the substantial proportion requiring

surgical or endovascular interventions illustrate the life-threatening and recurrent nature of the disease. Despite aggressive interventions, the incidence of fatal arterial ruptures remains significant, highlighting the limitations of current management strategies.

Conservative management with medical therapy and surveillance, applied in a subset of patients, demonstrates that non-invasive approaches remain necessary in selected cases, particularly when surgical risks are prohibitive. Collectively, the figure reinforces that vEDS is a severe, multisystem vascular disorder with early onset, high morbidity, and significant mortality. These findings emphasize the need for early recognition, proactive surveillance, individualized risk stratification, and multidisciplinary management to optimize outcomes and reduce catastrophic events. Additionally, the data support ongoing research into genotype–phenotype correlations, targeted therapies, and novel procedural techniques tailored to the unique vascular fragility in vEDS patients.

Table 1: Complications and Outcomes in Adults with vEDS and Circulatory Involvement

Complications/Outcomes	Number of Patients (%)	Clinical Notes
Recurrent vascular events	50%	Multiple episodes of dissections, aneurysms, or ruptures
Surgical/Endovascular interventions	40%	High procedural risk due to vessel fragility
Fatal arterial ruptures	20%	Catastrophic outcomes despite supportive care
Conservative management (medical + surveillance)	30%	Focused on blood pressure control and monitoring

The table summarizes the major complications and outcomes observed in adult patients with vascular Ehlers-Danlos syndrome (vEDS) who presented with systemic circulatory involvement. Recurrent vascular events were the most frequent complication, affecting about 50% of patients, and included repeated arterial dissections, aneurysms, or ruptures. Approximately 40% of patients required surgical or endovascular interventions to manage these events, although the procedures carried high risks due to the inherent fragility of blood vessels in vEDS. Despite intervention, complications during or after procedures were common, reflecting the challenges in managing such fragile vasculature.

The table also highlights the severity of outcomes in this population. Catastrophic arterial ruptures led to fatal outcomes in around 20% of patients, even with supportive care. In contrast, 30% of patients were managed conservatively with medical therapy, such as strict blood pressure control and routine imaging surveillance, which helped avoid invasive procedures. This balance between invasive and conservative strategies underscores the complexity of decision-making in vEDS management, where the risks of intervention must be weighed against the potential for life-threatening vascular events. Overall, the table reflects both the high burden of complications and the limited but essential role of preventive medical care in improving survival and quality of life for vEDS patients.

DISCUSSION

Despite increasing recognition of vascular Ehlers-Danlos syndrome (vEDS) as a distinct clinical entity, substantial challenges remain in optimizing diagnosis, management, and long-term care. One of the most pressing barriers is the heterogeneity of clinical presentation, which often overlaps with other connective tissue disorders and contributes to misdiagnosis. Subtle phenotypic features, such as thin translucent skin, characteristic facial features, or early-onset varicosities, may be overlooked in the absence of a major vascular event. This highlights the need for standardized diagnostic algorithms that integrate clinical suspicion, advanced imaging, and genetic testing at the earliest stage of evaluation.

Recent developments in genomic medicine have opened avenues for precision care in vEDS. Whole-exome sequencing, next-generation sequencing panels, and even RNA-based diagnostic tools are increasingly used to identify both known and novel COL3A1 variants. Beyond diagnosis, there is growing interest in the functional characterization of mutations for example, distinguishing between glycine substitutions, splicing variants, and null alleles to better predict clinical trajectories. Animal models and induced pluripotent stem cell (iPSC) studies are providing insight into the molecular mechanisms of collagen III dysfunction, offering potential targets for gene-editing therapies, RNA-based treatments, or molecular chaperones aimed at stabilizing collagen assembly.

Advances in non-invasive vascular imaging, including high-resolution MRI angiography and low-dose CT protocols, are enabling safer longitudinal monitoring of fragile vasculature. Artificial intelligence (AI)-based image analysis tools are also being investigated for early detection of micro-aneurysms and subtle vessel wall

changes, which may precede catastrophic events. Optimizing the frequency of surveillance remains an active area of research, as excessive imaging carries risks, yet insufficient monitoring may delay life-saving interventions.

Current pharmacologic strategies, though promising, remain empiric and underpowered by limited clinical trial data. Cicloprolol, in particular, has been associated with reduced vascular event rates in some studies, but its availability is geographically limited and long-term efficacy data are still emerging. Broader evaluation of other pharmacologic classes, including renin-angiotensin system inhibitors and novel Vaso protective agents, is warranted.

From an interventional perspective, surgical and endovascular approaches remain high-risk, as vessel fragility predisposes patients to rupture and poor wound healing. Innovative strategies, such as custom stent designs, atraumatic catheter systems, and hybrid procedures, are under development to minimize procedural risks. Decision-making requires a delicate balance between conservative management and timely intervention, often necessitating multidisciplinary input from vascular surgeons, geneticists, cardiologists, and radiologists.

The psychological burden of vEDS is profound, given the unpredictability of vascular events and the limitations imposed on daily activities. Integrating mental health services, peer support networks, and palliative care principles can help address anxiety, depression, and uncertainty [1]. Special considerations are also required for reproductive health, as pregnancy in women with vEDS carries heightened risk of arterial rupture, uterine rupture, and maternal mortality. Pre-pregnancy counselling, high-risk obstetric care, and multidisciplinary monitoring are essential components of care [2] [3][18].

Given the rarity of vEDS, international registries and multicentre collaborations are indispensable to advance knowledge and develop evidence-based guidelines. Large-scale, prospective studies are needed to refine risk prediction models, validate genotype–phenotype associations, and assess the efficacy of medical and interventional therapies. Furthermore, the integration of biomarker research, including circulating collagen degradation products or endothelial dysfunction markers, may provide minimally invasive tools for monitoring disease activity and progression.

Ultimately, progress in vEDS care will depend on cross-disciplinary collaboration, spanning genetics, vascular biology, imaging science, bioengineering, and patient advocacy. By combining cutting-edge molecular technologies with patient-centred clinical care, there is potential to move beyond supportive management toward truly disease-modifying therapies that can alter the natural history of this devastating condition.

CONCLUSION

This study highlights the complex clinical spectrum of vascular Ehlers-Danlos syndrome (vEDS) in adult patients presenting with systemic circulatory complications. The findings confirm that arterial dissections, aneurysms, and spontaneous ruptures are the most frequent and life-threatening manifestations. Demographic analysis revealed that most patients were diagnosed in early adulthood, often after a severe vascular event, emphasizing the diagnostic delays commonly associated with this rare condition. Despite genetic confirmation and improved imaging techniques, outcomes remained limited due to the inherent fragility of the vascular system in vEDS. The clinical implications of this study reinforce the importance of early recognition, proactive surveillance, and multidisciplinary management of vEDS patients. Non-invasive imaging, strict blood pressure control, and careful consideration of surgical or endovascular interventions are essential to minimize complications. Healthcare providers must remain vigilant when evaluating young patients with unexplained vascular events and prioritize early genetic testing to confirm the diagnosis. Patient centred care, including counselling, preventive strategies, and family screening, is critical to improving survival and quality of life in this high-risk population. Future research should focus on developing safer and more effective therapeutic strategies tailored to the unique vascular fragility in vEDS. Long-term prospective studies are needed to evaluate the benefits of novel medical therapies, advanced imaging surveillance, and minimally invasive interventions. Additionally, research into molecular pathways and targeted treatments may provide new opportunities for reducing vascular complications. Expanding registries and collaborative studies will also be vital to improving understanding, refining clinical guidelines, and ultimately enhancing patient outcomes in vascular Ehlers-Danlos syndrome.

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